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L2: Entry 30 of 54

File: USPT

Aug 3, 1999

DOCUMENT-IDENTIFIER: US 5932462 A

**** See image for Certificate of Correction ****

TITLE: Multiarmed, monofunctional, polymer for coupling to molecules and surfaces

Detailed Description Text (115):

It should be recognized that there are thousands of proteins and enzymes that can be usefully modified by attachment to the polymer derivatives of the invention. Proteins and enzymes can be derived from animal sources, humans, microorganisms, and plants and can be produced by genetic engineering or synthesis. Representatives include: cytokines such as various interferons (e.g. interferon-.alpha., interferon-.beta., interferon-.gamma.), interleukin-2 and interleukin-3), hormones such as insulin, growth hormone-releasing factor (GRF), calcitonin, calcitonin gene related peptide (CGRP), atrial natriuretic peptide (ANP), vasopressin, corticotropin-releasing factor (CRF), vasoactive intestinal peptide (VIP), secretin, .alpha.-melanocyte-stimulating hormone (.alpha.-MSH), adrenocorticotrophic hormone (ACTH), cholecystokinin (CCK), glucagon, parathyroid hormone (PTH), somatostatin, endothelin, substance P, dynorphin, oxytocin and growth hormone-releasing peptide, tumor necrosis factor binding protein, growth factors such as growth hormone (GH), insulin-like growth factor (IGF-I, IGF-II), .beta.-nerve growth factor (.beta.-NGF), basic fibroblast growth factor (bFGF), transforming growth factor, erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), enzymes such as tissue plasminogen activator (t-PA), elastase, superoxide dismutase (SOD), bilirubin oxydase, catalase, uricase and asparaginase, other proteins such as ubiquitin, islet activating protein (IAP), serum thymic factor (STF), peptide-T and trypsin inhibitor, and derivatives thereof. In addition to protein modification, the two-armed polymer derivative of the invention has a variety of related applications. Small molecules attached to two-armed activated mPEG derivatives of the invention can be expected to show enhanced solubility in either aqueous or organic solvents. Lipids and liposomes attached to the derivative of the invention can be expected to show long blood circulation lifetimes. Other particles than lipids and surfaces having the derivative of the invention attached can be expected to show nonfouling characteristics and to be useful as biomaterials having increased blood compatibility and avoidance of protein adsorption. Polymer-ligand conjugates can be prepared that are useful in two phase affinity partitioning. The polymers of the invention could be attached to various forms of drugs to produce prodrugs. Small drugs having the multisubstituted derivative attached can be expected to show altered solubility, clearance time, targeting, and other properties.

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L2: Entry 19 of 54

File: USPT

Aug 28, 2001

DOCUMENT-IDENTIFIER: US 6281371 B1

TITLE: Lipopolyamines, and the preparation and use thereof

Brief Summary Text (86):

Apart from DNA, it is also possible for other macromolecules, such as, for example, PNA, peptides, peptoids or proteins, to be introduced into cells. For that purpose the macro-molecules may be coated with the lipopolyamines according to the invention per se, or may be incorporated in liposomes that comprise as components the lipopolyamines according to the invention, or may be adsorbed on the surface thereof, if a negative net charge exists. By bringing such aggregates into contact with cells, transport of those molecules through the cell wall occurs. Therapeutic peptides have a favourable effect on numerous diseases. Such peptides or proteins include, for example, lymphokines, interleukins, tumour necrosis factors or interferons, also growth factors, tissue plasminogen activator, factor VIII:c, granulocyte-macrophage colony-stimulating factor, erythropoietin, insulin, calcitonin, thymidine kinase and others. In addition toxic peptides, such as ricin, diphtheria toxin and others, may be used therapeutically with success in that way. Peptoids may also be used successfully as peptide analogues to prevent a rapid enzymatic degradation in the body.

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L2: Entry 4 of 54

File: USPT

Apr 27, 2004

DOCUMENT-IDENTIFIER: US 6726924 B2

TITLE: Oral liposomal delivery system

Brief Summary Text (11):

More recently, feasibility of oral liposomes for a variety of therapeutic uses has been demonstrated. Increased bioavailability of liposomally encapsulated superoxide dismutase (Regnault C., et al, Biopharm & Drug Disp 17,165-174, 1996) a potent antioxidant used in the treatment of radiation-induced fibrosis, which is poorly absorbed orally, from 14% (free) to 57% with liposomes with ceramides. Hypocalcemia was observed 1 h after the administration of liposomes loaded with 1 mg of calcitonin. (Arien a., et al, Pharm Research 12(9):1289-1292, 1995). This result was surprising because liposomes were presumed to be unstable against the action of bile salts, however they were able to partially protect the peptide from enzymatic degradation. In another study, recombinant human erythropoietin (Epo), used to treat renal anemia, was encapsulated in liposomes. Bioavailability of oral Epo is poor because it is a protein and broken down in the GI tract by proteolytic enzymes. Absorption and a long pharmacological effect and lag were observed, suggesting that liposomes were trapped in a site before entering the bloodstream, and eliciting a sustained release effect. (Maitani Y., J Pharm Sc 85(4):440-445, 1996).

Other Reference Publication (8):

Maitani et al., "Oral Administration of Recombinant Human Erythropoietin in Liposomes in Rats: Influence of Lipid Composition and Size of Liposomes on Bioavailablilty", Journal of Pharmaceutical Sciences, vol. 85, No. 4, Apr. 1996.

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L2: Entry 35 of 54

File: USPT

Feb 23, 1999

DOCUMENT-IDENTIFIER: US 5874075 A

TITLE: Stable protein: phospholipid compositions and methods

Detailed Description Text (4):

Contemplated for use in the practice of the present invention are a variety of proteins capable of transitioning into the molten globular state. Exemplary proteins contemplated are cytokines, including various hematopoietic factors such as the aforementioned G-CSF, GM-CSF, MGDF, M-CSF, the interferons (alpha, beta, and gamma), the interleukins (1-11), erythropoietin (EPO), fibroblast growth factor, stem cell factor, nerve growth factor, BDNF, NT3, platelet-derived growth factor, and tumor growth factor (alpha, beta). Other proteins may be evaluated for the ability to transition into the MGS. If the protein in question is capable of transitioning into the MGS, the protein in question may then be contacted with a negatively charged liposome vesicle and the stabilizing effects evaluated.

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File: JPAB

Sep 10, 1996

PUB-NO: JP408231417A

DOCUMENT-IDENTIFIER: JP 08231417 A

TITLE: LIPOSOME PREPARATION OF ERYTHROPOIETIN

PUBN-DATE: September 10, 1996

INVENTOR-INFORMATION:

NAME

COUNTRY

NAGAI, TSUNEJI

YONETANI, YOSHIE

ASSIGNEE-INFORMATION:

NAME

COUNTRY

CHUGAI PHARMACEUT CO LTD

APPL-NO: JP07226610

APPL-DATE: September 4, 1995

INT-CL (IPC): A61 K 38/22; A61 K 9/127; A61 K 47/24; A61 K 47/28; C07 K 14/505

ABSTRACT:

PURPOSE: To obtain liposome which can include erythropoietin having actions to regulate the proliferation and differentiation of erythrocyte precursor cells in high inclusion efficiency and protects these actions.

CONSTITUTION: This liposome preparation includes erythropoietin(Epo). As a lipid for forming the vesicular wall of the liposome, dipalmitoyl phosphatidylcholine is preferably used. In addition, in order to sustain the activity of Epo, sterol (SA) and/or sterol glycoside (SAG) is formulated to the lipid. Preferred SA is β -sitosterol, campesterol, stigmasterol, brassicasterol and/or cholesterol, while the SAG is preferably a monoglycoside of either one of these sterols. The liposome is obtained by using a mixture of the lipid and SA and/or SAG to include Epo by the reverse-phase evaporation.

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